RENAL FUNCTION IN CHRONIC LIVER DISEASE

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of

MD (GENERAL MEDICINE) Branch – I

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL

Chennai

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

MARCH 2010

CERTIFICATE

This is to certify that the dissertation entitled "**RENAL FUNCTION IN CHRONIC LIVER DISEASE**" is the bonafide original work of **Dr. BETSY ANNIE KOSHY**, in partial fulfillment of the requirements for M.D BRANCH – I (General medicine) Examination of the TamilNadu Dr. M.G.R. Medical University Chennai to be held in MARCH 2010

Signature of Unit Chief **Signature of Prof. & HOD**

Signature of the Dean

DECLARATION

I solemnly declare that the dissertation titled "**RENAL FUNCTION IN CHRONIC LIVER DISEASE**" was done by me at Stanley Medical College and Hospital during 2008-2009 under the guidance and supervision of **PROF. S. RAMASAMY, M.D.,** Professor and Head of Department of Medicine.

The dissertation is submitted to the Tamil Nadu Dr. MGR Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE (BRANCH-I) in General Medicine.

Place: Chennai

Date: **Dr. BETSY ANNIE KOSHY**

ACKNOWLEDGEMENT

I thank **Prof. Dr. A. PRIYA, M.S., D.O,** Dean, Government Stanley Medical College and Hospital for allowing me to avail the facilities needed for my dissertation work.

I have great pleasure in expressing my deep sense of gratitude and respect to my respected teacher and unit chief **Prof. S. RAMASAMY, M.D.,** Professor and Head of the Department of Medicine, Stanley Medical College and Hospital, Chennai, for approving this study and giving suggestions and guidance in preparing this dissertation.

I am grateful to **Prof.V.JAYANTHI, M.D., D.M.,** Professor and Head of the Department of Medical Gastroenterology, Stanley Medical College for permitting me to do the study and for her encouragement.

I am extremely thankful to my assistant professors, **DR.S.ASHOK KUMAR, M.D., DR.S.GEETHA, M.D., DR.G.VASUMATHI, M.D.** Registrar, Department of Medicine

and all my colleagues, especially Dr. S. Hariharan for their valuable guidance and constant encouragement.

Finally, I wish to thank all the patients without whom this study would not have been possible.

CONTENTS

INTRODUCTION

The interrelationship between liver disease and renal dysfunction was recognized as early as the era of Hippocrates and this has been the object of a considerable amount of research since then.

Kidney dysfunction in liver disease can be due to different etiologies and can have diverse manifestations. Most of the abnormalities of kidney function in cirrhosis are of functional origin- namely, sodium retention, impaired free water excretion and renal vasoconstriction with decrease in renal perfusion and glomerular filtration rate. Renal dysfunction in chronic liver disease usually follows a progressive course – the final phase being Hepatorenal syndrome (HRS).

There is no explanation that fully defines the complex relationship between the diseased liver and disturbances in kidney function, though substantial progress is being made in recent years regarding research in this aspect.

One of the most difficult issues in the clinical evaluation of patients with cirrhosis is the accurate assessment of renal function.

Standard measures of renal function like blood urea nitrogen and serum creatinine are likely to give erroneous impressions and hence alternative methods to determine renal reserve must be used.

Detection of renal insufficiency is clinically important because it contributes significantly to high morbidity and mortality in cirrhosis. Moreover, renal dysfunction is one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after transplantation, as compared with those without renal failure.

AIM

- To determine the usefulness of serum creatinine and creatinine clearance as parameters in assessing renal function abnormalities in patients with chronic liver disease.

- To find if etiology of chronic liver disease has a bearing on renal dysfunction.

REVIEW OF LITERATURE

HISTORY

The first description of disturbances in renal function in chronic liver diseases was made by Frerichs and Flint in two independent reports from the late nineteenth century[1]. These reports described the development of oliguria in patients with chronic liver disease in the absence of proteinuria and with a normal renal histology, and proposed the first pathophysiologic interpretation of hepatorenal syndrome by linking the abnormalities of renal function to the disturbances present in the systemic circulation.

The coexistence of renal impairment and liver disease has even been mentioned by Hippocrates[2]; Helwig and Schutz introduced the term hepatorenal syndrome in 1932 when they described a patient with renal failure and biliary tract disease[3]. The detailed clinical description of HRS, however, was not made until the 1950s in studies by Sherlock, Papper, and Vessin.

RENAL ABNORMALITIES IN LIVER DISEASE

The mechanism underlying the development of renal dysfunction in advanced liver disease and cirrhosis is complex and includes interactions between changes in the systemic arterial circulation, portal hypertension, activation of vasoconstrictors and suppression of vasodilatory factors acting on the renal circulation.

Patients with advanced liver disease are susceptible to prerenal failure primarily due to disturbances in circulatory function- mainly, a reduction in systemic vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension[(4)]. The cause of this arterial vasodilatation is increased production or activity of vasodilator factors (particularly nitric oxide, carbon monoxide, and endogenous cannabinoids).

Another factor further exacerbating renal dysfunction in these patients is true hypovolemia, which can be induced by gastrointestinal tract hemorrhage from varices; peptic ulcers or gastropathy; excessive diuresis; vomiting and diarrhea; or can be aggravated by large volume paracentesis without intravascular volume replacement. Bacterial infections (eg. spontaneous bacterial peritonitis) and the use of

nonsteroidal anti-inflammatory drugs can also precipitate pre-renal failure in these patients. Development of septic shock is another possible event which may further impair renal function.

A) SODIUM RETENTION AND ASCITES/EDEMA

It is the first manifestation of renal impairment in cirrhosis. The total amount of sodium retained is dependent on the balance between sodium intake and excretion. Patients may develop ascites or edema when sodium intake is increased (high sodium diet or administration of intravenous saline solution) or when they are treated with drugs that increase sodium reabsorption, (such as mineralocorticoids or NSAIDS.)

The underlying mechanism responsible for renal sodium retention is an increased renal tubular reabsorption of sodium in the proximal and distal tubules[5]. This occurs even in the presence of a normal or only moderately reduced GFR. The two main sodium retaining systems responsible are the renin- angiotensin- aldosterone system (RAAS) and the sympathetic nervous system (SNS). These are activated as a homeostatic response to circulatory dysfunction.

B) SOLUTE-FREE WATER RETENTION AND DILUTIONAL HYPONATREMIA

Hyponatremia occurs in nearly half of patients in hospital with cirrhosis and ascites, and is due to the excessive retention of solute-free water which results from the kidney's inability to excrete it normally.

Pathogenesis of solute-free water retention in cirrhosis seems to be related to three events:

Reduced delivery of filtrate to the ascending limb of the loop of Henle; a reduced renal synthesis of prostaglandins; and an increased secretion of anti-diuretic hormone.

The morbidity and mortality associated with hyponatremia is largely attributable to central nervous system disturbances. Altered steroid and peptide hormones in cirrhotic patients may contribute to the development of hyponatremia encephalopathy, symptoms of which overlap with hepatic encephalopathy and uremia[(6)].

The appearance of hyponatraemia in cirrhotic patients, long regarded as a poor prognostic sign, is now identified as a marker of unrecognized underlying impaired renal function.

C) RENAL VASOCONSTRICTION

Renal vasoconstriction leading to decreased renal perfusion is the renal functional abnormality that develops last in patients with cirrhosis and ascites. It is the consequence of the extreme underfilling of the systemic arterial circulation due to marked vasodilatation of the splanchnic circulation, which activates homeostatic vasoconstrictor systems, whose effect on the kidney vasculature cannot be counterbalanced by either renal or systemic vasodilators[7].

Renal vasoconstriction predisposes to the development of hepatorenal syndrome (HRS).

TYPES OF RENAL FAILURE IN PATIENTS WITH CIRRHOSIS

A. HYPOVOLEMIA-INDUCED RENAL FAILURE

Hypovolemia is usually due to gastrointestinal hemorrhage or to fluid losses- either renal losses because of excessive diuretic therapy; or gastrointestinal losses as a result of diarrhea from excessive lactulose administration or gastrointestinal infection. Renal failure occurs soon after the onset of hypovolemia.

B. PARENCHYMAL RENAL DISEASE

Parenchymal renal disease should be suspected as a cause of renal failure when proteinuria (>500 mg of protein/day), hematuria (>50 red cells/high-power field), or both are present and ideally should be confirmed by renal biopsy, if this procedure is not contraindicated.

The presence of renal tubular epithelial cells in the urine sediment favours the diagnosis of acute tubular necrosis.

C. DRUG-INDUCED RENAL FAILURE

Current or recent treatment with nonsteroidal anti-inflammatory drugs or aminoglycosides suggests drug-induced renal failure.

D. HEPATORENAL SYNDROME

Hepatorenal syndrome is an uncommon but potentially fatal complication of decompensated cirrhosis. It is a unique form of functional renal failure that often complicates advanced liver disease, hepatic failure or portal hypertension. It is characterized by intense constriction of the renal arterial vasculature with resulting oliguria and avid sodium retention.

The definition of HRS as proposed by International Ascites Club is,

"Hepatorenal syndrome is a clinical condition that develops in patients with chronic liver disease and advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney there is marked renal vasoconstriction that results in low GFR. There is also vasoconstriction in other vascular territories such as the muscle, spleen and brain. In the splanchnic circulation, there is an intense arteriolar vasodilatation that results in reduction of total systemic vascular resistance and arterial hypotension. A similar syndrome can also develop in the setting of acute liver failure." [8]

Hepatorenal syndrome may occur spontaneously or in response to some insult such as infection, hemorrhage, or overly vigorous diuresis.

The renal circulation in hepatorenal syndrome demonstrates several abnormalities:

- reduction of renal blood flow and glomerular filtration;

- vasoconstriction involving the branches of the main renal artery and other smaller arteries;

- cortical ischemia and instability.

There are two patterns of hepatorenal syndrome(HRS):

Type I HRS is characterized by a rapid and progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg/dl or a 50% reduction of the initial 24 hour creatinine clearance to a level lower than 20 ml/min in less than 2 weeks.

The dominant features of type I HRS are marked renal failure with oliguria or anuria and increased serum levels of urea and creatinine. This type of HRS is frequently seen in patients with alcoholic cirrhosis, especially when associated with alcoholic hepatitis, but it occurs in non-alcoholic cirrhosis as well. Precipitating factors include spontaneous bacterial peritonitis (SBP) and major surgical procedures.

Most patients show signs of severe liver failure with marked hyperbilirubinemia, low prothrombin activity, and encephalopathy. It follows a fulminant course with development of oliguria and is

associated with very poor prognosis, with death occurring within 1 month after presentation[4].

In contrast to type I, **type II HRS** is characterized by less severe and stable reduction of GFR that does not meet the criteria proposed for type I. Patients are usually in better clinical condition than those with type I HRS, and their survival expectancy is markedly longer. The clinical picture is one of moderate stable renal disease in a patient with diuretic-resistant ascites due to the combination of intense sodium retention, reduced GFR, and marked stimulation of antinatriuretic systems.

The diagnosis of HRS is one of exclusion and depends mainly on the level of serum creatinine, despite the fact that it does not provide an accurate reflection of GFR in patients with cirrhosis.

PATHOGENESIS OF HEPATORENAL SYNDROME

Hepatorenal syndrome is characterised by functional renal vasoconstriction that leads to a severe reduction in GFR with minimal renal histologic abnormalities. Function can be restored following correction of portal hypertension by liver transplantation or even when

the kidneys are removed and transplanted into a non-cirrhotic recipient[9].

The initial abnormality in hepatorenal syndrome is peripheral and splanchnic arterial vasodilatation triggered by portal hypertension. This vasodilatation initiates adaptive responses that stimulate renal vasoconstriction and renal sodium and water retention.

Various mechanisms which contribute to the pathogenesis of HRS are:

1. Renin-Angiotensin-Aldosterone system (RAAS)

The activation of RAAS is particularly intense in patients with hepatorenal syndrome.

Plasma aldosterone levels are increased in most cirrhotic patients with ascites and marked sodium retention. This is due to a stimulation of aldosterone secretion and not due to impaired degradation as the hepatic clearance of aldosterone is normal or only slightly reduced in these patients.

It has also been suggested that cirrhotic patients may have an increased tubular sensitivity to aldosterone. This explains the renal

sodium retention even in patients with normal levels of aldosterone. Hence spironolactone, a specific aldosterone antagonist is able to reverse sodium retention and cause natriuresis in cirrhotics.

Plasma renin activity is also often elevated in patients with decompensated cirrhosis[10]. The role of angiotensin II is shown by the improvement of renal function in patients with HRS achieved by the administration of vasopressin analogues ornipressin or terlipressin associated with albumin, which causes a marked suppression of RAAS activity.

2. Sympathetic Nervous System

Patients with hepatorenal syndrome have significantly higher plasma levels of norepinephrine than do patients without renal failure; and this correlates inversely with renal blood flow; suggesting that the sympathetic nervous system may participate in the renal vasoconstriction observed in patients with hepatorenal syndrome.

Moreover, the circulating levels of neuropeptide Y, a neurotransmitter with a very potent vasoconstrictor action in the renal circulation released in the setting of a marked activation of the

sympathetic nervous system, are increased in patients with hepatorenal syndrome but not in those with ascites without renal failure.

3. Prostaglandins

Patients with hepatorenal syndrome have lower urinary excretion of PGE2 and PGI2 than do patients with ascites without renal failure, which suggests that a reduced renal synthesis of vasodilator prostaglandins may play a role in the pathogenesis of HRS[(9)]. As prostaglandins are potent vasodilators in the systemic circulation, an increased systemic prostaglandin synthesis may contribute to arterial vasodilatation in cirrhosis.

Moreover, a decrease in GFR and renal plasma flow by non steroidal anti-inflammatory drugs points towards a role of prostaglandin in maintaining normal renal perfusion.

It has also been postulated that an imbalance between vasodilator and vasoconstrictor metabolites of arachidonic acid, with the latter dominating, contributes to irreversible vasoconstriction characterising HRS

4. Adenosine

Intrahepatic adenosine causes an increase in portal venous blood flow and triggers a hepatorenal reflex (to regulate sodium and water excretion) which by means of increasing sympathetic activity in the kidney, leads to a decrease in renal blood flow and GFR[11]. This mechanism has been recently proposed which may lead to decreased renal perfusion and hepatorenal syndrome. Increased synthesis of adenosine may be accounted by tissue hypoxia due to advanced hepatic dysfunction.

5. Natriuretic Peptides

The plasma concentration of major natriuretic hormones, namely, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), is increased in patients with cirrhosis and ascites[9]. These high levels are due to enhanced cardiac release and not due to a reduced hepatic or systemic clearance. As these peptides have powerful effects on renal function (mainly vasodilator and natriuretic effects) and inhibit renin release, increased levels may act as a homeostatic mechanism to counteract the effects of anti-natriuretic and vasoconstrictor systems in the renal circulation.

But the existence of increased plasma levels of ANP in cirrhosis, in the presence of renal sodium retention, indicates a renal resistance to the effects of ANP.

6. Nitric oxide

Nitric oxide (NO) is a powerful vasodilator agent released from vascular smooth muscle. It has been proposed to be an important effector responsible for splanchnic vasodilation in cirrhosis. NO plays a role in the regulation of glomerular microcirculation by modulating the arteriolar tone and the contractility of mesangial cells. It facilitates natriuresis in response to changes in renal perfusion pressure and regulates renin release.

It was found in a study that NO increased significantly with progression of liver disease especially in the decompensated cirrhotic group[(12)]. This result supports that NO is important in the progression of cirrhosis. As a result, with an increase in NO with progression of the liver disease, especially in ascitic cirrhosis, renal tubular and glomerular functions are negatively affected.

7. Endothelin

The circulating levels of endothelin-1, an endothelial derived peptide with potent vasoconstrictor effect are also increased in cirrhosis probably due to an enhanced release of the peptide from the hepatic and/or splanchnic circulation. It has been proposed that the increased circulating levels and /or enhanced intrarenal production of endothelin may induce vasoconstriction of the renal circulation and play a role in the pathogenesis of hepatorenal syndrome.

8. Endotoxins

In cirrhotic patients the entire gastrointestinal tract becomes densely colonized with bacteria, presumably because of the patient's immunosuppressed status. Jaundice commonly observed in cirrhosis can promote reabsorption of endotoxin into the bloodstream. As the reticuloendothelial cells of the liver are likely to be compromised in advanced cirrhosis, absorbed endotoxin would not be completely destroyed by the hepatic Kupffer cells and would appear in the arterial circulation. The continuous reabsorption of endotoxin from the gastrointestinal tract into the circulation of patients with advanced cirrhosis leads to vasoconstriction of the renal microcirculation[13].

In summary, peripheral vasodilatation is the early event in the pathogenesis of fluid retention and hepatorenal syndrome. Following initial vasodilatation, maintanence of normal renal perfusion depends on a balance between vasodilatory and vasoconstricting factors. Hepatorenal syndrome represents an imbalance favouring vasoconstrictive over vasodilating factors, the consequences of which are a marked increase in renal vascular resistance, decrease in GFR, and avid sodium and water retention

DIAGNOSTIC CRITERIA FOR HEPATORENAL SYNDROME[14]

MAJOR CRITERIA

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension

2. Low glomerular filtration rate as indicated by serum creatinine of >1.5mg/dl or 24 hour creatinine clearance <40ml/min

3. Absence of treatment with nephrotoxic drugs, shock, infection or significant recent fluid losses

4. No sustained improvement in renal function after diuretic withdrawal and volume expansion with 1.5 L of isotonic saline

5. Proteinuria < 0.5 g per dL and no ultrasonographic evidence of obstruction or parenchymal renal disease

ADDITIONAL CRITERIA

1. Urine volume <500 ml/day
2. Urine sodium <10mEq/L
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cells <50 per high power field
5. Serum sodium concentration < 130mEql/L

PSEUDO-HEPATORENAL SYNDROME

There are various conditions in which both liver and kidneys are affected, but in which the liver disease does not play an etiological role in the pathogenesis of renal failure. These conditions constitute the so-called "pseudo-hepatorenal syndrome"[15].

CAUSES OF PSEUDO-HEPATORENAL SYNDROME

1. Congenital – Polycystic disease, sickle cell anaemia, congenital hepatic fibrosis, nephronophthisis
2. Toxic agents – Drugs: tetracycline, halothane, acetaminophen, sulphonamides, rifampicin, allopurinol, phenytoin, methoxyflurane, methotrexate(high dose); and other toxic agents: carbon tetrachloride poisoning in industrial workers, chloroform, arsenic, barium
3. Infections – Miliary tuberculosis, hepatitis B, hepatitis C, HIV, Schistosomiasis, septicaemia, yellow fever, leptospirosis
4. Connective tissue disorders- SLE, Sjogren's syndrome
5. Circulatory alterations – Shock, heart failure
6. Unknown aetiology – Amyloidosis, sarcoidosis,
7. Reye's syndrome

TREATMENT OF HEPATORENAL SYNDROME

Many different therapeutic approaches have been proposed for the management of hepatorenal syndrome. Unfortunately, most treatment measures result in only transient beneficial effects on renal function, and are not consistently associated with improvement in patient survival.

Liver transplantation remains the definitive treatment for hepatorenal syndrome; recovery of renal function is typical after that. In patients with either type 1 or type 2 HRS, the prognosis is poor unless transplant can be achieved within a short period of time.

Transplantation in hepatorenal syndrome is associated with higher hospital mortality compared to those without HRS who are treated with transplantation[16]. Thus, every attempt should be made to prevent this severe complication or reverse it when managing patients with cirrhosis and ascites.

In recent years, new treatment strategies such as the use of vasoconstrictor drugs with preferential effect on the splanchnic circulation(V1 receptor agonists), along with plasma volume expansion, or insertion of TIPS, have been used with promising results. These treatments may prolong survival time and, therefore, act as a bridge to

liver transplantation in these patients. Vasoconstrictors used for hepatorenal syndrome include vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenalin)[17]. In type 1 hepatorenal syndrome terlipressin in combination with albumin has shown to result in greater improvement in renal function compared to terlipressin alone[18]. Pharmacological treatment, when combined with interventional techniques, such as transjugular intrahepatic portosystemic shunt (TIPS), may further improve renal function in hepatorenal syndrome. However, TIPS is frequently associated with significant side effects, particularly hepatic encephalopathy and impairment of liver function[19], and its role in the management of hepatorenal syndrome needs to be established by prospective, controlled investigations.

The molecular adsorbent recirculating system (MARS) has been used in the treatment of acute decompensation of chronic liver disease, acute liver failure and hepatorenal syndrome. This liver support system utilizes either intermittent (6-8 h daily) or continuous hemodialysis with dialysate enriched with 20% human serum albumin as a means to

remove albumin-bound toxins (bilirubin, bile acids, fatty acids, tryptophan, aromatic amino acids, and copper)[20].

EVALUATION OF PATIENTS WITH CIRRHOSIS AND RENAL FAILURE

Renal function should be routinely monitored in all patients with advanced cirrhosis, especially those with ascites. Patients who have ascites, particularly those with hyponatremia, bacterial infections, gastrointestinal bleeding, or severe sodium retention, are at high risk for renal failure, as are all patients hospitalized for acute decompensation of cirrhosis[21].

Other than blood urea nitrogen, serum creatinine and creatinine clearance, evaluation of renal function should also include

Serum electrolytes	-	hyponatremia is common; potassium sparing diuretics shpuld be discontinued to precvent hyperkalemia ;
Urine analysis	-	significant proteinuria and urine sediment abnormalities usually indicate parenchymal renal disease

Renal ultrasonography	-	abnormal renal ultrasonograms indicate chronic parenchymal renal disease
Renal biopsy	-	helpful when parenchymal renal disease is suspected because of proteinuria, hematuria, or both and is also helpful in deciding on simultaneous kidney transplantation in candidates for liver transplantation. Renal biopsy is contraindicated if severe coagulation abnormalities are present.

The evaluation of patients with cirrhosis and renal failure should also include an assessment of liver function, as well as the exclusion of possible bacterial infections. The patient’s medications should be reviewed, and diuretics should be discontinued, since these agents may either be the cause of renal failure or contribute to the impairment of renal function.

DIFFERENTIAL DIAGNOSIS OF RENAL FAILURE IN LIVER DISEASE

The differential diagnosis of renal dysfunction in advanced liver disease includes pre-renal failure, intrinsic renal failure and hepatorenal syndrome.

The diagnostic evaluation relies upon clinical and laboratory data, including urine analysis, as well as ultrasonographic and radiological investigations.

Renal biopsy generally is not necessary for the diagnosis of acute renal failure in liver disease, but is useful in excluding an intrinsic renal disorder[22]. A history of gastrointestinal hemorrhage, vomiting or diarrhea, exposure to nephrotoxic medication, or features suggestive of sepsis may provide important diagnostic information.

Arterial hypertension, which is an unexpected finding in patients with cirrhosis, suggests glomerulonephritis. Purpura, arthralgia, weakness, Raynaud's syndrome, or leg ulcers suggest cryoglobulinemia associated with hepatitis C. The presence of antibodies to hepatitis C virus and hepatitis C virus RNA, high concentrations of cryoglobulins, positive rheumatoid factor assays, and low concentrations of

complement suggest hepatitis C virus-associated cryoglobulinemic glomerulonephritis[23].

Diagnostic information may be obtained from urine analysis. Pigmented granular casts are typical of ischemic and toxic acute renal failure and red cell casts of glomerulonephritis. Patients with renal azotemia due to acute or subacute glomerulonephritis have significant proteinuria (around 3 g/d). In contrast, proteinuria is absent or moderate in other causes of acute renal failure.

Urine indices such as osmolality, sodium concentration, urine:plasma osmolality ratio (U/Posm) and urine:plasma creatinine ratio (U/Pcreat), are useful theoretical tools for differential diagnosis of the three principal causes of acute renal failure in liver disease.

TABLE I

DIFFERENTIATION OF HRS FROM PRE-RENAL AZOTEMIA AND ACUTE TUBULAR NECROSIS (ATN)[24,25]

Differentiating characteristic	HRS	Pre-renal azotemia	Acute tubular necrosis
History of precipitating event	May/ may not be present	Invariably present; loss of fluids evident	Present with fluid loss, shock, sepsis, or nephrotoxic drugs
Urine output	Oliguria	Oliguria	Oliguria, anuria
Urinary sediment	Absent	Hyaline casts	Granular casts, cellular debris
Urinary sodium (meq/l)	< 5	< 10	> 20
Urine to plasma osmolality ratio	> 1.5	> 1.5	1
Urine to plasma creatinine ratio	> 40	> 40	< 20
Response to plasma expansion	Absent	Good	Absent

The course of renal response to fluid challenge or vasoconstrictor therapy can also help differentiate causes of acute azotemia in liver disease. Rapid improvement in renal function in response to fluid challenge denotes pre-renal failure, whereas mild or no improvement represents acute tubular necrosis or hepatorenal syndrome. Vasoconstrictor agents such as terlipressin or noradrenalin can sometimes be used to differentiate between hepatorenal syndrome and acute tubular necrosis, with improvement of GFR in favour of hepatorenal syndrome[26].

Duplex Doppler ultrasonography, is another sensitive method of assessing intrarenal hemodynamics in patients with cirrhosis and ascites, in whom the renal artery resistive index is significantly increased and correlates with GFR and plasma renin activity[27].

PROGNOSIS OF RENAL FAILURE IN CIRRHOSIS

The prognosis for patients with cirrhosis and renal failure is poor[28]. The overall survival rate is approximately 50 % at 1 month and 20 % at 6 months .This extremely poor outcome is probably related to the combination of liver and renal failure, as well as to associated complications.

However, survival rates can differ according to the type of renal failure. The hepatorenal syndrome is associated with the worst prognosis. The great majority of patients with hepatorenal syndrome have a poor short-term outcome unless they undergo liver transplantation. Mortality is higher with type 1 hepatorenal syndrome than with type 2 (median survival, 1 month vs. 6 months).

PREVENTION OF RENAL FAILURE IN ADVANCED LIVER DISEASE

Two different strategies can be used to prevent hepatorenal syndrome.

The first is to perform liver transplantation in patients with cirrhosis and ascites before hepatorenal syndrome develops. The identification of factors associated with a high risk of developing HRS and the use of duplex Doppler ultrasonography to assess the renal artery resistive index in the follow-up of these patients may be useful for this purpose.

The second strategy is to prevent the development of renal impairment in patients by avoiding the precipitating factors i.e. prompt management of bleeding and infection.

Spontaneous bacterial peritonitis is a precipitating factor of HRS. SBP stimulates the production of the proinflammatory cytokine, tumor necrosis factor-alpha, which is known to induce vasorelaxant mechanisms in arteries[29]. Thus, the SBP induced TNF–mediated activation of vasodilator mechanisms may enhance preexisting systemic vasodilation (and arterial hypovolemia) and precipitate hepatorenal syndrome. It has been hypothesized that in patients with SBP, simultaneous intravenous administration of albumin and antibiotics could prevent the sepsis-induced decrease in effective arterial blood volume and resulting HRS.

A recent study has indicated that the development of hepatorenal syndrome in patients with SBP can be effectively prevented by the addition of albumin to antibiotic (cefotaxime) therapy (1.5 g/kg human albumin intravenously at the time of diagnosis of the infection and 1 g/kg intravenously 48 hr later)[30]. The proportion of patients who developed HRS and the in-hospital mortality was significantly lower in the cefotaxime-plus-albumin group than in the cefotaxime alone. The beneficial effect of albumin is probably related to its ability to prevent circulatory dysfunction and subsequent activation of vasoconstrictor systems that occur during infection[30].

OTHER RENAL ABNORMALITIES IN CIRRHOSIS

- GLOMERULAR DISEASES

In association with hepatitis B and C viruses and alcoholic liver disease

- RENAL TUBULAR ACIDOSIS

May occur in cirrhosis of different etiologies: primary biliary cirrhosis, autoimmune hepatitis and alcoholic cirrhosis

- DRUG INDUCED RENAL DYSFUNCTION

Especially with NSAIDs, aminoglycosides, diuretics or vasodilators

- ACUTE TUBULAR NECROSIS

Due to volume depletion as in sepsis or hypovolemic shock or due to nephrotoxic drugs

- IMPAIRED SODIUM AND POTASSIUM EXCRETION

MATERIALS AND METHODS

INCLUSION CRITERIA

This study included patients with chronic liver disease being treated as in-patients in the Department of General Medicine, Government Stanley Hospital, Chennai.

Evidence for chronic liver disease being defined by:

- a compatible Clinical profile (signs of liver cell failure or reduced liver span) along with

  Biochemical (altered liver function tests, reversal of albumin-globulin ratio) or

  Sonographic evidence (altered echotexture of liver)

  OR

- Tissue diagnosis (positive liver biopsy for cirrhosis)

EXCLUSION CRITERIA

- Elderly patients (>60 years)
- Overt renal failure (S. creatinine >1.5)
- Known primary renal disease
- Diabetes mellitus / Hypertension
- Grade 4 hepatic encephalopathy
- Recent gastrointestinal bleed

METHODOLOGY

Inpatients in the medical ward/IMCU admitted with chronic liver disease with seemingly normal renal function were included in this analytical study which was conducted from June 2009 to October 2009.

Data regarding demographic variables (age, weight), clinical features (presenting complaints, ascites, jaundice, encephalopathy, history of alcoholism, etc) and clinical examination findings of liver cell failure were collected using a proforma (attached in Annexure).

Diuretics were withheld for 3 days before carrying out lab investigations.

Lab investigations including complete Liver function test, Renal function tests, Viral marker for hepatitis B, Urine analysis, 24 hour urine volume and Urine creatinine was done and results noted.

Patients were subjected to an ultrasound scan of abdomen with regard to liver echotexture and size, evidence of splenomegaly or portal hypertension, presence of ascites and kidney pathology.

Creatinine clearance for the patient was calculated by the formula (URINE CREATININE / SERUM CREATININE MULTIPLIED BY 24 HOUR URINE VOLUME).

$$(U_{Cr} / P_{Cr}) \times V$$

This was divided by 1440 to get the value in ml/minute.

Creatinine clearance was also calculated using the Cockcroft and Gault formula(CGF).

(140- AGE) x WEIGHT / (SERUM CREATININE x 72)

This value is to be multiplied by 0.85 if the patient is female.

Comparison between serum creatinine and creatinine clearance calculated by these two methods were done.

OBSERVATIONS AND ANALYSIS

50 patients with chronic liver disease were enrolled in the study. 7 patients did not satisfy inclusion criteria and were excluded. So, a total of 43 patients were included.

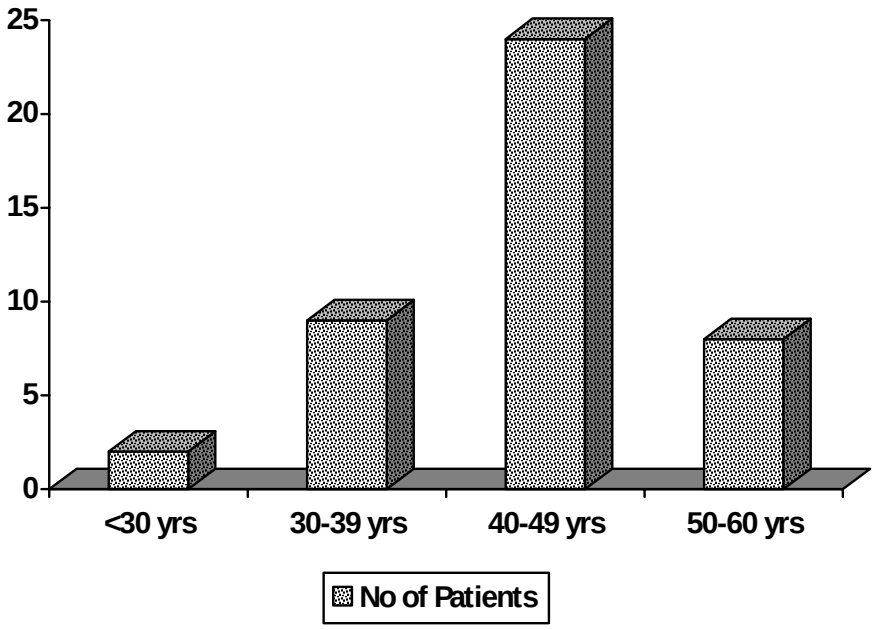
The following observations were made:

AGE AND SEX:

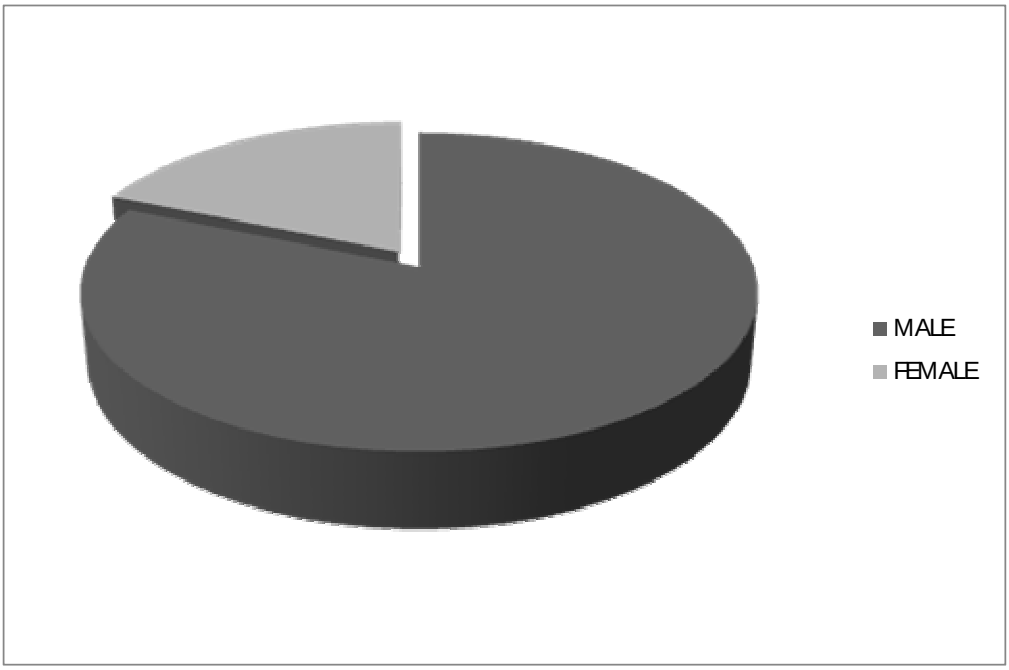
Age of the patients ranged from a minimum of 22 years to a maximum of 58 years. The mean age was 42.14 years. The age distribution is as follows:

AGE GROUP	NUMBER OF PATIENTS
Less than 30 years	2
30 to 39 years	9
40 to 49 years	24
Above 50 years	8

Patients above 60 years were excluded as GFR decreases with age. False low GFR thus calculated would interfere with the findings of this study.



Of the patients included in the study 35 were male, while remaining 8 were female.

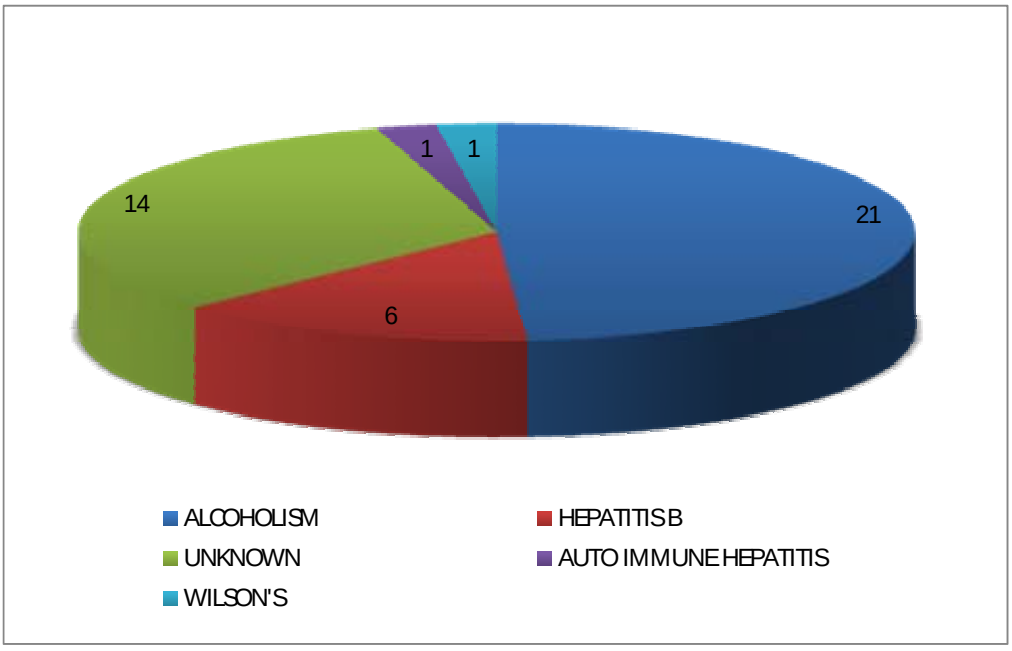


ETIOLOGY:

Out of the 43 patients of cirrhosis, the cause of liver disease was attributed to alcoholism in 21 patients. 6 patients were found to be positive for Hepatitis B surface antigen. One patient was a case of Wilson's disease and another patient was found to have autoimmune hepatitis.

In the other 14 patients, causative etiology could not be ascertained.

ETIOLOGY	NO. OF PATIENTS	PERCENTAGE
ALCOHOLISM	21	48.83 %
HEPATITIS B	6	13.95 %
WILSON'S	1	2.33 %
AUTO IMMUNE HEPATITIS	1	2.33 %
UNKNOWN	14	32.56 %



ASSESSMENT OF RENAL FUNCTION BY DIFFERENT METHODS

Out of the 43 patients, renal function was assessed by serum creatinine, creatinine clearance from timed urine collection [(UxV)/P] and creatinine clearance by Cockcroft Gault formula(CGF).

The patients were grouped into three based on their creatinine clearance [(UxV)/P]. Group I having values more than 60 ml/mt, Group II 30-60 ml/mt and Group III less than 30 ml/mt.

	GROUP I	**GROUP II**	**GROUP III**
BLOOD UREA mg/dL	22.43	22.42	22.4
SERUM CREATININE mg/dL	0.90	1	1.2
24 HOUR URINE VOLUME ml	2010.71	1136.84	690
CREATININE CLEARANCE (UxV / P) ml/mt	85.33	43.41	18.55
CREATININE CLEARANCE (CG FORMULA) ml/mt	85.02	63.87	44.90

BLOOD UREA LEVELS

There was no significant variation in blood urea levels in all the three groups, suggesting that estimation of blood urea will not be of much use in determining renal impairment.

Mean blood urea level was 22.42 mg/dL.

SERUM CREATININE

Only patients with creatinine levels less than 1.5 mg/dL were included in this study. It was seen that in 7 patients with creatinine clearance less than 30 ml/mt, serum creatinine levels failed to rise above 1.2 mg/dL, suggesting that moderate to severe renal dysfunction may be masked by seemingly normal creatinine levels.

The mean serum creatinine level was 1.01 mg/dL.

24 HOUR URINE VOLUME

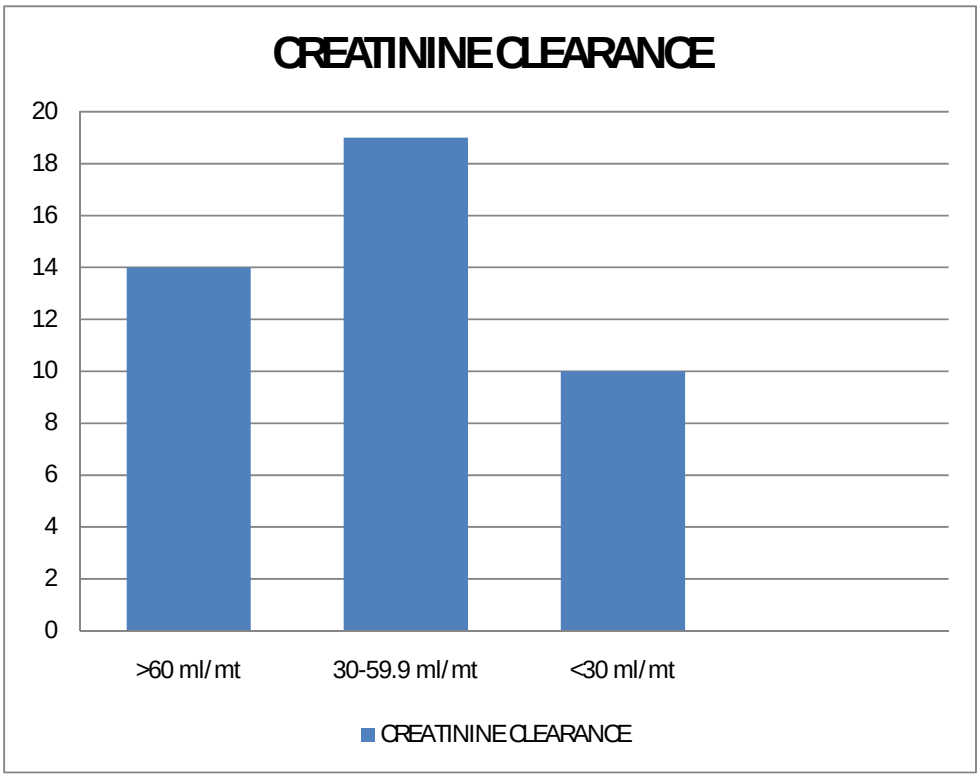
Patients with greater amount of renal impairment were found to have lesser urine output, thus suggesting that eliciting history of oliguria in a patient with normal serum creatinine levels should call for a high index of suspicion of renal dysfunction.

The mean 24 hour urine volume was 1317.44 ml.

MEASURED CREATININE CLEARANCE BY TIMED URINE COLLECTION:

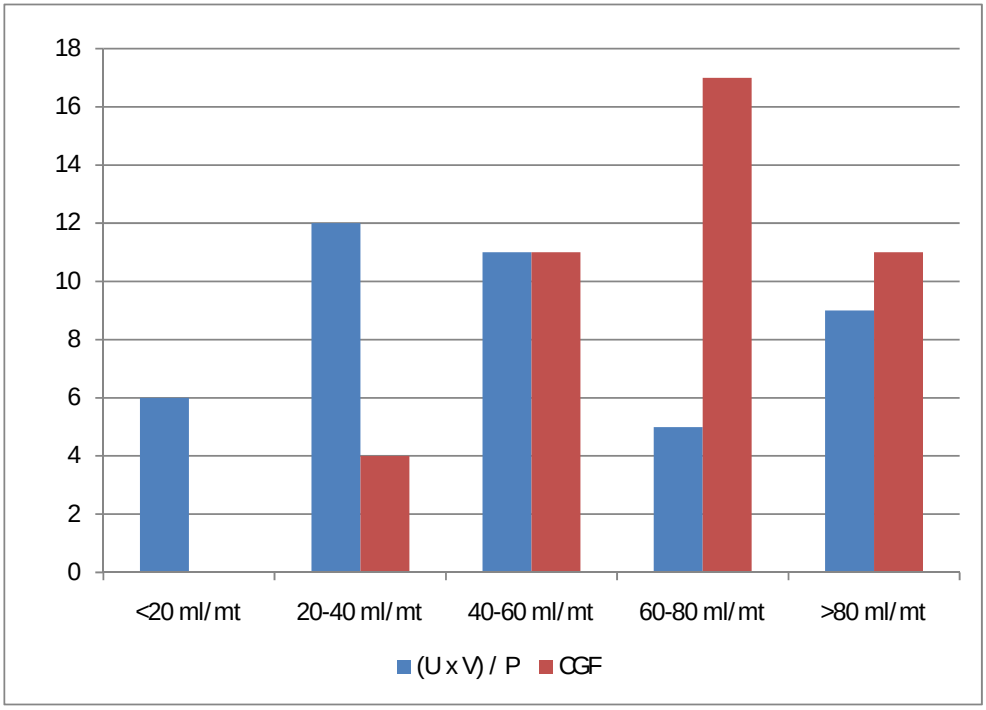
The patients were grouped into three based on their creatinine clearance:

Group	Creatinine clearance	No. of patients
Group I	>60 ml/minute	14
Group II	30-60 ml/minute	19
Group III	<30 ml/minute	10



Measurement of creatinine clearance using the Cockcroft Gault formula (CGF) showed significantly higher values, suggesting overestimation of GFR by this method.

CREATININE CLEARANCE	BY (U x V) / P	BY COCKCROFT GAULT FORMULA
<20 ml/mt	6 (13.95 %)	0 (0 %)
20-40 ml/mt	12 (27.90 %)	4 (9.30 %)
40-60 ml/mt	11 (25.58 %)	11 (25.58 %)
60-80 ml/mt	5 (11.63 %)	17 (39.54 %)
>80 ml/mt	9 (20.93 %)	11 (25.58 %)



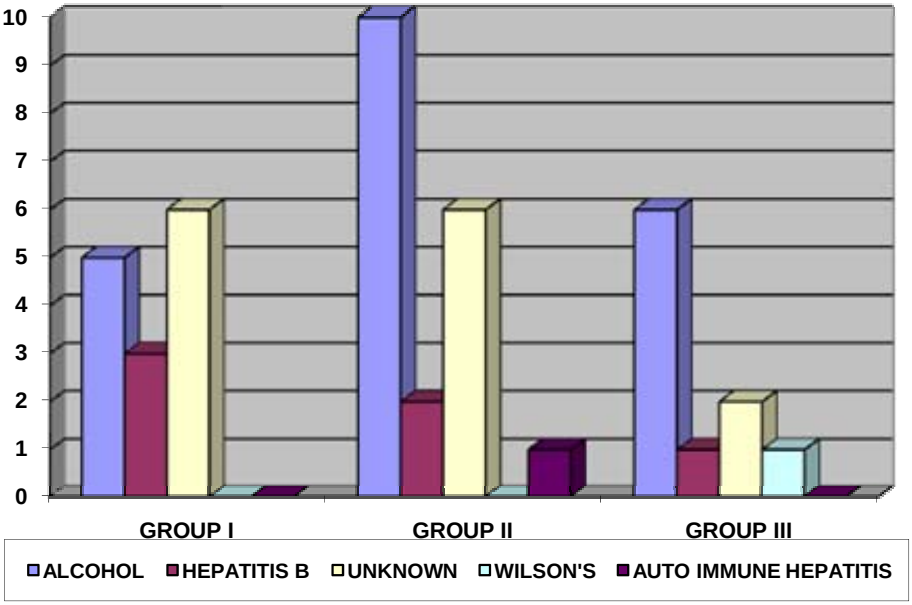
Eighteen percent ie, five out of the twenty-eight patients with creatinine clearance more than 60 ml / minute by Cockcroft gault formula were found to have creatinine clearance values less than 40 ml/minute when done by timed urine collection.

P value calculated was found to be less than 0.0001 which is statistically significant.

RENAL FUNCTION ACCORDING TO ETIOLOGY

ETIOLOGY	NUMBER OF PATIENTS		
	GROUP I	GROUP II	GROUP III
ALCOHOLISM	5	10	6
HEPATITIS B	3	2	1
WILSON'S	0	0	1
AUTO IMMUNE	0	1	0
UNKNOWN	6	6	2

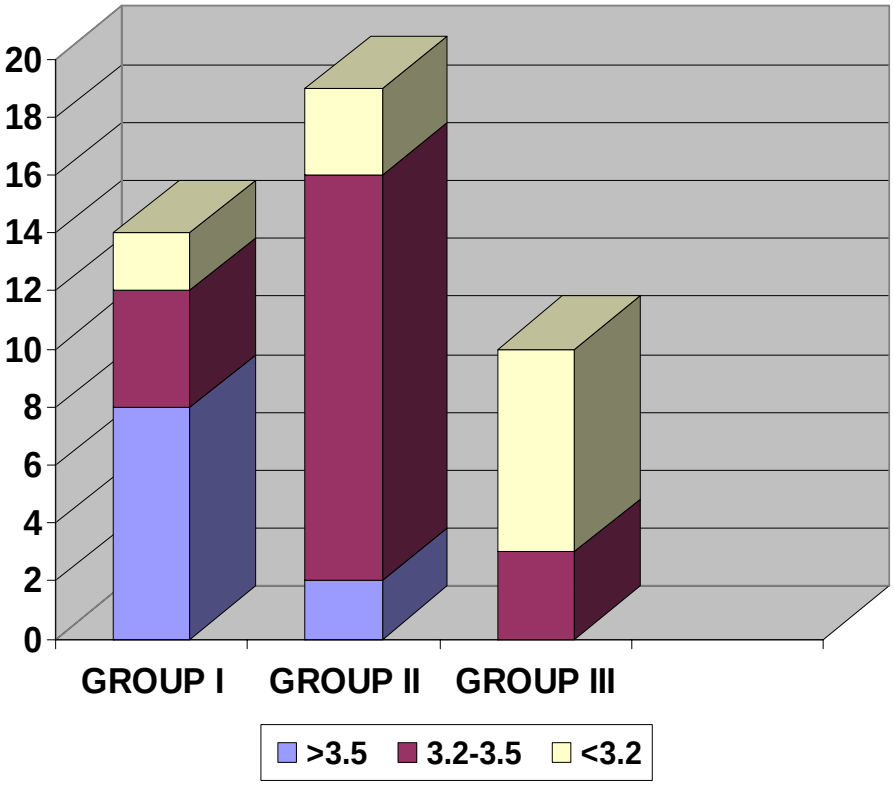
Out of the 21 alcoholic liver disease patients, only 5 (20 %) had creatinine clearance more than 60 ml/minute, whereas 3 (50%) out of the 6 HBsAg positive patients had creatinine clearance more than 60 ml/minute.



SERUM ALBUMIN AND RENAL FUNCTION

Mean serum albumin was 3.37 mg/dL. The distribution of serum albumin in the three groups was as follows:

SERUM ALBUMIN (mg/dL)	GROUP I	GROUP II	GROUP III
>3.5	8	2	0
3.2-3.5	4	14	3
<3.2	2	3	7



Average serum albumin (mg/dL) in the three groups was:

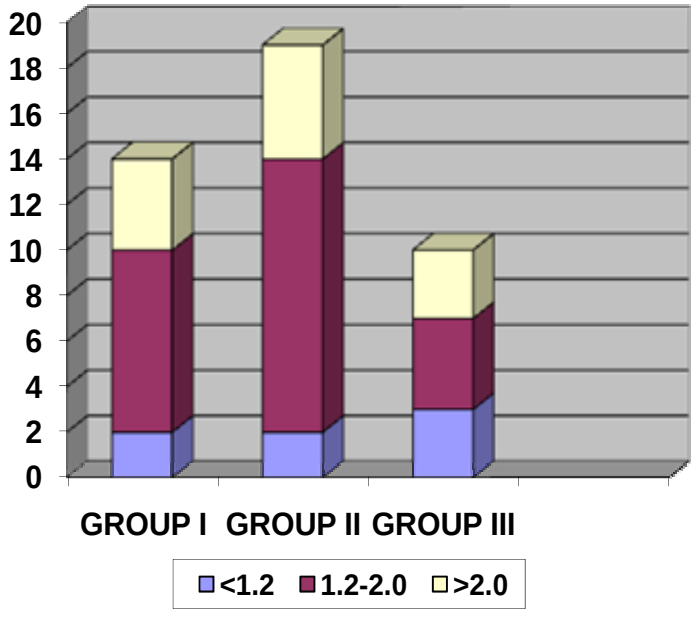
GROUP I	-	3.59
GROUP II	-	3.34
GROUP III	-	3.11

Serum albumin was found to have direct correlation with renal function, ie, patients with higher rates of creatinine clearance were seen to have higher albumin levels.

SERUM BILIRUBIN AND RENAL FUNCTION

The distribution of serum bilirubin levels in the three groups were as follows:

SERUM BILIRUBIN (mg/dL)	GROUP I	GROUP II	GROUP III
< 1.2	2	2	3
1.2 – 2	8	12	4
> 2	4	5	3



The mean bilirubin was 1.64 mg/dL. Average bilirubin levels in the 3 groups:

Group I - 1.67

Group II - 1.61

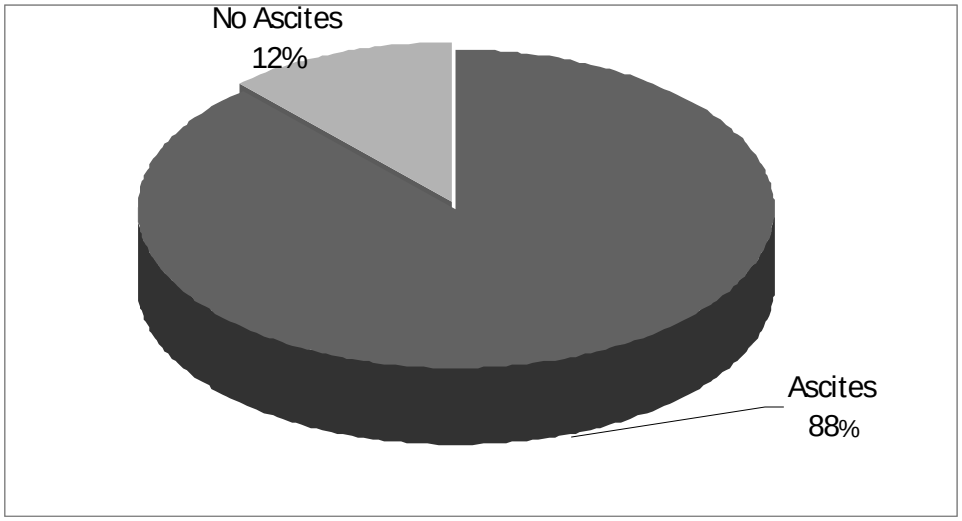
Group III - 1.64

Serum bilirubin levels were found to have no significant correlation with renal function.

ULTRASOUND FINDINGS

Ultrasound abdomen was done in all of the 43 patients. Findings of splenomegaly and altered echotexture of liver were uniformly seen in all these patients.

Ascites was present in 38 out of the 43 patients. It was noted that the patients without ascites had relatively better renal function; ie, all the 5 patients belonged to group I (Creatinine clearance > 60 ml/mt). thus suggesting that ascites may be one of the first changes in worsening renal function.



Liver was shrunken in size in 41 of the study subjects. The remaining 2 showed changes of malignant transformation.

Kidney size and corticomedullary differentiation was normal in all patients.

DISCUSSION

This study followed 43 patients with chronic liver disease with special emphasis on renal function.

Many patients with cirrhosis and ascites will have a glomerular filtration rate of less than 60 ml/minute but a normal serum creatinine level. Our study showed that serum creatinine alone in patients with advanced liver disease is of limited value for identification of renal dysfunction. This is in agreement with the findings in a study by **McAulay et al[31].**

Another prospective study of a large number of cirrhotic patients by **Papadakis and Arieff** also indicated that the glomerular filtration rate can be very low even when the serum creatinine is less than 1.0 mg/dL[32].

The level of serum creatinine required for the diagnosis of HRS is 1.5 mg/dL, in the absence of diuretic therapy. Although this value may seem rather low, patients with cirrhosis and a serum creatinine above 1.5 mg/dL have a GFR below 30 ml/min[33]. Hence, patients with creatinine levels more than 1.5 mg/dL were excluded from our study.

Our study also shows that calculating creatinine clearance by Cockcroft Gault formula overestimates renal function. This is probably due to discrepancies in weight due to fluid retention which is one of the consequences of renal impairment in cirrhotics. As weight is one of the variables in the numerator of the formula, an increase in weight due to edema or ascites will give a spuriously high creatinine clearance. The study by **McAulay** also supports this finding[31]. This overestimation of renal function was highest in patients with lower GFR, which was observed in our study also.

MacAulay et al observed that among the Cr-based GFR formulas, the MDRD formula had the best overall accuracy. This formula developed by the Modification of Diet in Renal Disease (MDRD) Study Group is based on the patient's Creatinine levels, age, sex, race and serum urea nitrogen and serum albumin levels and it showed a larger proportion of agreement with radionuclide GFR in patients with advanced liver disease. MacAulay summarised that in clinical practice, the MDRD is the best formula for detection of moderate renal dysfunction among those with cirrhosis[31]. But the above mentioned study didn’t include any formulas requiring urine collection. As MDRD formula requires web based calculations, it will be

impractical to rely on it as a parameter of assessing renal function in a resource limited setup.

Measured creatinine clearance from timed urine collections is a relatively inexpensive, accessible method used in clinical practice. Our study showed that it provides a better estimate of renal reserve than serum creatinine or predicted creatinine clearance by Cockcroft-Gault formula.

A systematic review and meta-analysis of patients with cirrhosis by **Proulx et al** showed that although creatinine clearance measured by timed urine collections overestimates GFR in patients with liver cirrhosis, it is a preferable method in clinical practice, as it is more reliable than serum creatinine or predicted creatinine clearance (by CGF)[33]. This overestimation is substantial especially in the low GFR range where important decisions relative to drug dose adjustment, the staging of CKD and the pre-liver transplant evaluation may be required.

The meta-analysis proved that direct measurement of GFR using inulin clearance (CIn) is the most accurate estimate of renal reserve[34]. But in routine clinical practice, GFR estimation by this method is not

very feasible because of the complexity, expense and limited availability of testing and overall patient inconvenience.

Few articles have examined alternative GFR markers using cystatin C or radioisotopes and two studies support the use of the renal clearance of either [^{51}Cr]EDTA or [^{125}I]iothalamate to estimate GFR in patients with liver cirrhosis, which again will be impractical in our setup.

The study by **Papadakis and Arrief** was a prospective evaluation of 23 non-azotemic cirrhotic patients with ascites over a three-year interval[(32)]. It showed that the serum creatinine levels frequently failed to rise above normal even when the glomerular filtration rate was very low (less than 25 ml/minute), and creatinine clearance overestimated inulin clearance. However, this study also suggested that creatinine clearance was an aid in determining true glomerular filtration rate(when inulin clearance was not available) and may be a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values.

Our study has shown a direct correlation between serum albumin levels and renal function. This may also indicate that renal dysfunction is more with advancing classes of Child-Pugh classification. The correlation with albumin levels has also been noted in a study by **Amrapurkar et al[35].** This latter study also denoted direct correlation between chronicity of liver disease and renal dysfunction. It also showed a higher mortality in patients with lower creatinine clearance especially with hepatorenal syndrome.

But a study by **Hampel et al** showed no significant difference in serum levels of albumin and did not consider it as a risk factor for renal dysfunction[36]. The same study showed no significant differences in age, etiology of cirrhosis, serum levels of bilirubin, prothrombin time, encephalopathy, bacteremia, urinary tract infection, or occurrence of esophageal variceal bleeding in cirrhotic patients with or without renal dysfunction. Patients who developed renal dysfunction were more likely to have ascites. This was seen in our study also.

The study by **Hampel et al** also showed aminoglycoside treatment as a strong risk factor for renal dysfunction, independent of the severity of liver disease or spontaneous bacterial peritonitis[36].

Our study showed that patients with alcoholic liver disease were predisposed to develop renal impairment when compared with liver disease of other etiologies. Only 20 % of alcoholic patients had a creatinine clearance of more than 60 ml/mt as compared to 50 % of cirrhotic patients due to hepatitis B.

Our study showed that standard measures of renal function, namely blood urea and serum creatinine should not be the only criteria to assess renal reserve in chronic liver disease, as they may seem normal even in gross renal dysfunction.

Blood urea nitrogen levels may also vary in the absence of GFR changes. The reasons for this being :

1) Blood urea levels may be lower than expected in patients with liver disease because of reduced hepatic synthesis.

2) Blood urea levels may also increase because of gastrointestinal hemorrhage or catabolic states.

Hence, blood urea levels cannot be relied on to assess renal dysfunction.

Similarly, serum creatinine measurements may underestimate changes in GFR[37] because of

1) decreased synthesis of creatine from liver, and more importantly,

2) decreased endogenous production of creatinine in cirrhotics due to decreased muscle mass as a result of severe wasting.

Hence, to check for renal dysfunction in advanced liver disease, routine tests like blood urea and serum creatinine will be insufficient. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status.

CONCLUSIONS

- In chronic liver disease, serum creatinine alone is not a reliable marker to assess renal dysfunction.

- Calculating creatinine clearance by using Cockcroft Gault formula overestimates renal function in cirrhotics.

- Creatinine clearance measured by timed urine collections should be done routinely to assess renal reserve in advanced liver disease.

- Alcoholism appears to have adverse effect on renal function when compared with other etiologies of cirrhosis.

BIBLIOGRAPHY

1. Flint A. Clinical report on hydroperitoneum based on an analysis of forty-six cases. Am J Med Sci 1863;45: 306-39.

2. Atkinson M. Ascites in liver disease. Postgraduate Med J 1956;32: 482-85.

3. Helwig FC, Schutz CB. A liver-kidney syndrome: clinical, pathological and experimental studies. Surg Gynecol Obstet 1932;55: 570-80.

4. Betrosian AP, Agarwal B, Douzinas EE. Acute renal dysfunction in liver diseases. World J Gastroenterol 2007;13(42): 5552-59.

5. Cardenas A, Arroyo V. Mechanisms of sodium and water retention in liver cirrhosis. Best Pract Res Clin Endocrinol Metab 2003;17: 602-22.

6. Papadakis MA, Fraser CL, Arieff AI. Hyponatraemia in Patients with Cirrhosis. Q J Med 1990;76: 675-88.

7. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis; a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8: 1151-57.

8. Arroyo V, Gines P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23: 164-76.

9. Domurat ES, Elias AN. The endocrinology and pathophysiology of alcoholic cirrhosis and functional renal failure. J Natl Med Assoc 1992;84: 153-62.

10. Schroeder ET, Eich RH, Smulvan H, et al. Plasma renin level in hepatic cirrhosis. Am J Med 1970;49: 186-91.

11. Ming Z, Smyth DD, Lautt WW. Decrease in portal flow trigger a hepatorenal reflex to inhibit renal sodium and water excretion in rats: role of adenosine. Hepatology 2002;35: 167-75.

12. Turkay C, Yonem O, Arikan O, Baskin E. Nitric oxide and renal functions in liver cirrhosis. Turk J Gastroenterol 2004;15(2): 73-76.

13. Bercoff E, Le Bihan G, Caline M, Lemeland JF and Bourreille J. Do endotoxins play a part in renal impairment of cirrhosis? The Lancet 1981 May;317(8229): 1097-98

14. Feldman M, Friedman LS, Sleisenger MH. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 7th ed. 2002:1543-54.

15. Prakash A, Kubba S, Singh NP, Agarwal SK. Anasarca in a Non-Cirrhotic Portal Fibrosis Patient after Spleno-Renal Shunt Procedure. Journal Indian Academy of Clinical Medicine 2003;4(4): 282-5.

16. Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. Transplantation 1995;59: 361-365

17. Cardenas A. Hepatorenal syndrome: a dreaded complication of end-stage liver disease. Am J Gastroenterol 2005;100: 460-67

18. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol 2003;18: 152-56

19. Ochs A. Transjugular intrahepatic portosystemic shunt. Dig Dis 2005;23: 56-64.

20. Stange J, Hassanein TI, Mehta R, Mitzner SR, Bartlett RH. The molecular adsorbents recycling system as a liver support system based on albumin dialysis: a summary of preclinical investigations, prospective, randomized, controlled clinical trial, and clinical experience from 19 centers. Artif Organs 2002;26: 103-10.

21. Gines P, Schrier RW. Renal failure in cirrhosis. New England Journal of Medicine 2009 Sep;361(13) :1279-89.

22. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003;37: 233-43.

23. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996;334: 1448-60.

24. Brady HR, Brenner BM. Acute renal failure. In: Braunwald E, Fauci AS, Kasper DL et al (eds.) Harrison’s principles of Internal Medicine. New York: McGraw Hill, 15th edn, 2001; pp 1541-51.

25. Chung RT, Podolsky DK. Cirrhosis and its complications. In: Braunwald E, Fauci AS, Kasper DL et al (eds.) Harrison's principles of Internal Medicine. New York: McGraw Hill, 15th edn, 2001; pp 1754-66.

26. Duvoux C, Zanditenas D, Hezode C, Chauvat A, Monin JL, Roudot-Thoraval F, Mallat A, Dhumeaux D. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology 2002;36: 374-80.

27. Maroto A, Gines A, Salo J, Claria J, Gines P, Anibarro L, Jimenez W, Arroyo V, Rodes J. Diagnosis of functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. Hepatology 1994;20: 839-44.

28. Fasolato S., Angeli P., Dallagnase L., et al. Renal failure and bacterial infections in patients with cirrhosi: epidemiology and clinical features. Hepatology 2007;45: 223-9

29. Navasa M, Follo A, Filella X, Jimeenez W, Francitorra A, Planas R, Rimola A, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. HEPATOLOGY 1998;27: 1227-1232

30. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35: 1179-85

31. MacAulay J, Thompson K, Kiberd B A, Barnes D C, Peltekian K M. Serum creatinine in patients with advanced liver disease is of limited value for identification of moderate renal dysfunction: Are the equations for estimating renal function better? The Canadian journal of gastroenterology 2006 Aug;20(8): 521-26.

32. Papadakis M A, Arieff A I. Unpredictability of clinical evaluation of renal function in cirrhosis: A prospective study. The American Journal of Medicine 1987 May;82(5): 945-52.

33. Bataller R, Gines P, Guevara M, Arroyo V: Hepatorenal syndrome. Semin Liver Dis 1997;17: 233-48.

34. Proulx N L, Akbari A, Garg A X, Rostom A, Jaffey J, Clark H D. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. Nephrol Dial Transplant 2005;20: 1617–22.

35. Amrapurkar D N, Dhawan P , Kalro R H. Role of routine estimation of creatinine clearance in patients with liver cirrhosis. Indian J. Gastroenterol 1994;13(3): pg 79-82.

36. Hampel H, Bynum G D, Zamora E, El-Serag H B. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. The American Journal of Gastroenterology 2001 July;96(7): 2206-10.

37. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: Problems and pitfalls. American Journal of Kidney Diseases 2003 Feb;41(2): 269-78.

PROFORMA

1. NAME:

2. AGE:

3. SEX:

4. WEIGHT (IN KG):

5. ETIOLOGY OF CHRONIC LIVER DISEASE:

   ALCOHOLISM/ HEPATITIS B/ WILSON'S/ AUTOIMMUNE HEPATITIS/ UNKNOWN

6. CLINICAL FEATURES:

   -JAUNDICE/ HEMETEMESIS/ MALENA/ ABDOMINAL DISTENSION/ PEDAL EDEMA/ DECREASED URINE OUTPUT/ FEVER OR OTHER SIGNS OF SBP

   -ASCITES/ HEPATOMEGALY/ SPLENOMEGALY/ SIGNS OF LIVER CELL FAILURE

7. HISTORY OF ALCOHOLISM: YES/ NO

8. INVESTIGATIONS:

   - LIVER FUNCTION TESTS-

     SERUM BILIRUBIN

TOTAL PROTEIN

SERUM ALBUMIN

SGOT/SGPT

- RENAL FUNCTION TESTS-

  BLOOOD UREA NITROGEN

  SERUM CREATININE (P)

  SERUM ELECTROLYTES

- URINE ANALYSIS-

  24 HOUR URINE VOLUME (V)

  24 HOUR URINE CREATININE (U)

- CREATININE CLEARANCE-

  1. (U x V) / (P x 1440)
  2. COCKCROFT GAULT FORMULA

     (140-AGE) x WEIGHT / (P x 72)

     X .85 (IF FEMALE)

- HBsAG- POSITIVE/ NEGATIVE

- ULTRASOUND ABDOMEN-

    LIVER – SIZE/ ECHOTEXTURE

    SPLEEN- SIZE

    ASCITES

    KIDNEYS-

        SIZE

        CORTICOMEDULLARY DIFFERENTIATION

MASTER CHART

S. No	NAME	Age	Sex	Wgt	Etio	S.Br	T.Pr	S.Alb	BUN	S.Cr	24Hr Ur	Ur.Cr	CR CL	CR CL	USG ABD			
										P	V	U	(U x V) / P	(CGF)	Asc	Lvr	Sply	Kidy
1	Jayavel	32	M	50	HepB	1.5	7	4	22	0.8	1900	54.00	89.06	93.75	Y	S	Y	N
2	Suresh	40	M	58	X	1.8	6	3	22	1	2000	57.50	79.86	80.56	Y	S	Y	N
3	Munusamy	40	M	60	Alc	1.2	6.8	3.7	26	0.9	1950	60.75	91.41	92.59	Y	S	Y	N
4	Lakshmanan	38	M	52	HepB	1	6.4	3.8	20	0.8	2100	49.50	90.23	92.08	N	S	Y	N
5	Ibrahim	42	M	70	X	1.3	6.9	3.6	26	1	2300	65.00	103.82	95.28	N	S	Y	N
6	Rajavelu	40	M	55	Alc	1	7	4	18	1	2500	49.00	85.07	76.39	N	S	Y	N
7	Malaikonda	45	M	48	Alc	1.6	6	3.5	22	0.8	1700	53.00	78.21	79.17	Y	S	Y	N
8	Pichaiya	43	M	55	X	1.4	6.5	3.8	28	0.9	2000	55.00	84.88	82.33	Y	S	Y	N
9	Chandra	44	F	58	X	2	6	3.5	22	0.8	1900	50.00	82.47	82.17	N	S	Y	N
10	Loganathan	40	M	60	Alc	2.2	6.2	3.6	18	0.9	1800	58.00	80.56	92.59	Y	S	Y	N
11	Fathima	38	F	56	HepB	1.8	6.4	3.8	20	1	2000	57.00	79.17	79.33	Y	S	Y	N
12	Murugesan	40	M	58	X	1.2	6.1	3.1	22	0.8	2200	55.00	105.03	100.69	N	S	Y	N
13	Kuppusamy	42	M	50	Alc	3	6.2	3.5	26	1	1900	52.00	68.61	68.06	Y	S	Y	N
14	Jayanthi	41	F	58	X	2.4	6	3.4	22	0.9	1900	52.00	76.23	75.32	Y	S	Y	N
15	Rajan	44	M	53	Alc	2	5.8	3.4	28	0.8	1500	46.00	59.90	88.33	Y	S	Y	N
16	Palayam	38	M	49	X	1	6.2	3	24	1	900	56.00	35.00	69.42	Y	S	Y	N
17	Kumari	45	F	55	X	1.4	6	3.5	20	0.8	1300	44.00	49.65	77.11	Y	S	Y	N
18	Irulandi	50	M	61	Alc	1.7	5.5	3.2	22	1	800	63.00	35.00	76.25	Y	S	Y	N
19	Selvam	40	M	50	Alc	0.8	6	3.3	18	0.8	1000	57.50	49.91	86.81	Y	S	Y	N
20	Tamizhselvan	42	M	49	Alc	1.5	5.8	3.4	20	1	1500	53.75	55.99	66.69	Y	S	Y	N
21	Arumugam	48	M	53	Alc	1.2	6	3.5	28	0.9	1400	46.25	49.96	75.25	Y	S	Y	N

S. No	NAME	Age	Sex	Wgt	Etio	S.Br	T.Pr	S.Alb	BUN	S.Cr	24Hr Ur	Ur.Cr	CR CL	CR CL	USG ABD			
										P	V	U	(U x V) / P	(CGF)	Asc	Lvr	Sply	Kidy
22	Subbaiya	38	M	45	HepB	1.6	6	3.2	22	1	750	61.50	32.03	63.75	Y	N	Y	N
23	Sivagami	50	F	50	X	2.3	6.2	3	24	1.4	1200	59.00	35.12	37.95	Y	S	Y	N
24	John	38	M	45	X	1.2	5.8	3.3	20	1	1250	64.50	55.99	63.75	Y	S	Y	N
25	Dilli Babu	50	M	50	Alc	2.6	6.2	3.5	18	1	900	56.00	35.00	62.50	Y	S	Y	N
26	Kesavan	45	M	47	Alc	1.4	5.6	3.2	26	1.2	1200	54.50	37.85	51.68	Y	S	Y	N
27	Kalaiselvi	38	F	35	AIH	2.4	6	3.4	28	0.8	950	55.00	45.36	52.68	Y	S	Y	N
28	Elumalai	40	M	40	Alc	1.6	6	3.6	26	1.2	1100	58.00	36.92	46.30	Y	S	Y	N
29	Jayapal	45	M	50	Alc	1.2	5.8	3.3	24	1	1300	47.00	42.43	65.97	Y	S	Y	N
30	Mohd. Iqbal	28	M	38	HepB	1.6	5.6	3.1	18	0.9	1200	55.00	50.93	65.68	Y	S	Y	N
31	Anbumani	30	M	40	X	1.4	5.8	3.3	22	1	1250	48.00	41.67	61.11	Y	S	Y	N
32	Palani	35	M	38	X	1.5	6.1	3.7	18	1	1100	58.00	44.31	55.42	Y	S	Y	N
33	Subramani	50	M	45	Alc	2.2	6.2	3.5	20	1.2	1000	55.00	31.83	46.88	Y	S	Y	N
34	Natarajan	46	M	41	Alc	1.2	5.8	3.1	24	1.2	500	45.50	13.17	44.61	Y	S	Y	N
35	Kannan	50	M	40	X	1.8	5.7	3	18	1.4	800	40.00	15.87	35.71	Y	S	Y	N
36	Nadiya	55	F	50	X	1.2	6	3.2	22	1.2	500	44.00	12.73	41.81	Y	S	Y	N
37	Elangovan	50	M	42	Alc	3.2	6	3.4	26	1.3	800	50.00	21.37	40.38	Y	S	Y	N
38	Velan	45	M	43	Alc	1	5.8	3	22	1.2	900	51.00	26.56	47.28	Y	S	Y	N
39	Santhosh	24	M	34	Wilsn	1.8	6.2	3.1	20	1.2	400	48.00	11.11	45.65	Y	S	Y	N
40	Guna	43	F	41	HepB	2	5.5	3	22	1	600	43.00	17.92	46.95	Y	N	Y	N
41	Ali Akbar	40	M	44	Alc	1	6	3.1	26	0.9	750	44.00	25.46	67.90	Y	S	Y	N
42	Karthikeyan	42	M	40	Alc	2.2	5.7	3.2	20	1.4	850	43.00	18.13	38.89	Y	S	Y	N
43	Shahul	58	M	42	Alc	1	5.8	3	24	1.2	800	50.00	23.15	39.86	Y	S	Y	N

KEY TO MASTER CHART

1. Name of patient

2. Age (in years)

3. Sex

4. Weight (in kg)

5. Etiology of chronic liver disease: Etio

Alcoholism	Alc
Hepatitis B	HepB
Wilson's	Wilsn
Autoimmune hepatitis	AIH
Unknown	X

6. Serum Bilirubin S. Br

7. Total Protein T. Pr

8. Serum Albumin S. Alb

9. Blood Urea Nitrogen BUN

10. Serum Creatinine (P)

11. 24 Hour Urine Volume (V)

12. Urine Creatinine (U)

13. Creatinine clearance CR CL

= (U x V) / (P x 1440)

14. Creatinine clearance (Cockcroft Gault formula CGF)

= (140 – age) x weight / (P x 72) x
0.85 if female

15. Ultrasound abdomen

Ascites (Asc)	Yes	Y
	No	N
Liver (Lvr)	Shrunken	S
	Normal	N
Splenomegaly (Sply)	Yes	Y
	No	N
Kidney (Kidy)	Normal	N